Personalised medicine? Don’t hold your breath

Stephen Senn
Acknowledgements

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A previous Prime Minister of the UK speaks

This agreement will see the UK lead the world in genetic research within years. I am determined to do all I can to support the health and scientific sector to unlock the power of DNA, turning an important scientific breakthrough into something that will help deliver better tests, better drugs and above all better care for patients....

David Cameron, August 2014 (my emphasis)
Genes, Means and Screens

It will soon be possible for patients in clinical trials to undergo genetic tests to identify those individuals who will respond favourably to the drug candidate, based on their genotype. This will translate into smaller, more effective clinical trials with corresponding cost savings and ultimately better treatment in general practice. … individual patients will be targeted with specific treatment and personalised dosing regimens to maximise efficacy and minimise pharmacokinetic problems and other side-effects.

Sir Richard Sykes, FRS, 1997

My emphasis

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Zombie statistics 1
Percentage of non-responders

What the FDA says

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Efficacy rate (%)</th>
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<tbody>
<tr>
<td>Alzheimer’s</td>
<td>30</td>
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Paving the way for personalized medicine, FDA Oct 2013

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Spear, Heath-Chiozzi & Huff, Trends in Molecular Medicine, May 2001

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Zombie statistics 2

Where they got it

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Where those who got it got it

The Real Truth

• These are zombie statistics
• They refuse to die
• Not only is the FDA’s claim not right, it’s not even wrong
• It’s impossible to establish what it might mean even if it were true
88.2% of all statistics are made up on the spot

Vic Reeves
59% had no headache after 2 hours when treated with paracetamol

49% had no headache after 2 hours when treated with placebo

59% - 49% = 10%

Therefore 10% benefitted

The number needed to treat for one extra patient to have a benefit is 10
‘It tells us we can help about 35% of migraine patients’
Painful comparison

Cochrane Collaboration meta-analysis

• Meta-analysis of placebo-controlled trials of paracetamol in tension headache
• 23 studies
• 6000 patients in total
• Outcome measure:
  – Pain free by 2 hours

Baayen *Significance* article

• Explanation of Novartis’s MCP-Mod dose-finding approach using a trial run by Merck
• 7 doses + placebo
• 517 patients in total
• Outcome measure
  – Pain free by 2 hours
In both cases

- The patients were only studied once
- A dichotomy of a continuous measure was made
- Patients were labelled as responders and non-responders
- A causal conclusion was drawn that went beyond simply comparing proportions
  - Baayen talked about the proportion of patients who would respond
  - Cochrane talked about the proportion of patients to whom it would make a difference in terms of response
What I propose to do

• Create a simple statistical model to mimic the Cochrane result
  – In terms of time to pain resolution every patient will have the same proportional benefit
    • In fact I shall be using a form of proportional hazards model
  – The dichotomy will classify patients as responders or non-responders
  – We will be tempted to conclude that some don’t benefit and some do and that this is a permanent feature of each patient
The Numerical Recipe

• I shall generate pain duration times for 6000 headaches treated with placebo
  – This will be done using an exponential distribution with a mean of just under 3 hours (2.97 hrs to be exact)
  – Each such duration will then be multiplied by just over \( \frac{3}{4} \) (0.755 to be exact) to create 6000 durations under paracetamol

• I shall then take the 6000 pairs and randomly erase one member of the pair to leave 3000 unpaired placebo values and 3000 unpaired paracetamol values

• I shall then analyse the data
Why this recipe?

- The exponential distribution with mean 2.970 is chosen so that the probability of response in less than two hours is 0.49
  - This is the placebo distribution
- Rescaling these figures by 0.755 produces another exponential distribution with a probability of response in under two hours of 0.59
  - This is the paracetamol distribution
Counterfactual: pain duration reduced by 1/4

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Dichotomania

- We lose information through such dichotomies
- We tend to believe our own nonsense labels
  - Response
  - Non-response
- We then delude ourselves that Nature also believes our nonsense
- Next stop: *personalised medicine*
However

• So far I have only gone half way in my simulation recipe
• I have simulated a placebo headache and a corresponding paracetamol headache
• However I can’t treat the same headache twice
• One of the two is counterfactual
• I now need to get rid of one member of each factual/counterfactual pair
Counterfactual experiment

Note log scale

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Probability of response to headache treatment

![Graph showing the probability of response to headache treatment over time for different treatments.]

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To sum up

• The results reported are perfectly consistent with paracetamol having the same effect on every single headache
• This does not have to be the case but we don’t know that it isn’t
• The combination of dichotomies and responder analysis has great potential to mislead
• Researchers are assuming that because some patients ‘responded’ in terms of an arbitrary dichotomy there is scope for personalised medicine
The Pharmacogenomic Revolution?

• Clinical trials
  – Cleaner signal
  – Non-responders eliminated

• Treatment strategies
  – “Theranostics”

• Markets
  – Lower volume
  – Higher price per patient day
Implicit Assumptions

• Most variability seen in clinical trials is genetic
  – Furthermore it is not revealed in obvious phenotypes
    • Example: height and forced expiratory volume (FEV₁) in one second
    • Height predicts FEV₁ and height is partly genetically determined but you
don’t need pharmacogenetics to measure height

• We are going to be able to find it
  – Small number of genes responsible
  – Low (or no) interactive effects (genes act singly)
  – We will know where to look

• We are going to be able to do something about it
  – May require high degree of dose flexibility

• In fact we simply don’t know if most variation in clinical trials is due to individual response let alone genetic variability

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## Sources of Variation in Clinical Trials

<table>
<thead>
<tr>
<th>Label</th>
<th>Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Between treatments</td>
<td>The difference between treatments averaged over all patients</td>
</tr>
<tr>
<td>B</td>
<td>Between patients</td>
<td>The difference between patients given the same treatment</td>
</tr>
<tr>
<td>C</td>
<td>Patient-by-Treatment Interaction</td>
<td>The extent to which the effect of treatment varies from patient to patient</td>
</tr>
<tr>
<td>D</td>
<td>Within patients</td>
<td>The extent to which the results vary from occasion to occasion for patients given the same treatment</td>
</tr>
</tbody>
</table>

# Identifiability and Clinical Trials

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Description</th>
<th>Identifiable Effects</th>
<th>Error Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel</td>
<td>Each patient is randomised to receive one treatment</td>
<td>A</td>
<td>B+C+D</td>
</tr>
<tr>
<td>Cross-over</td>
<td>Each patient receives each treatment in one period only</td>
<td>A and B</td>
<td>C+D</td>
</tr>
<tr>
<td>Repeated cross-overs</td>
<td>Each patient receives each treatment in at least two periods</td>
<td>A and B and C</td>
<td>D</td>
</tr>
</tbody>
</table>
Giving this medicine to children:
It is important to know how much your child weighs to make sure you give them the correct amount of medicine. As a guide a child of 9 years of age will weigh about 30 kg (four and a half stone). If in doubt weigh your child, then follow the instructions in the table.

Do not give to children who weigh less than 30 kg.
Do not give to children under 2 years.

<table>
<thead>
<tr>
<th>Age</th>
<th>How many to take</th>
<th>How often to take</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and children of 12 years and over</td>
<td>One tablet</td>
<td>Once a day</td>
</tr>
<tr>
<td>Children of 2 to 11 years who weigh more than 30 kg</td>
<td>One tablet</td>
<td>Once a day</td>
</tr>
<tr>
<td>Children of 2 to 11 years who weigh less than 30 kg</td>
<td>Do not give this medicine. For children over 2 years of age and who weigh less than 30 kg a syrup form of this medicine may be more suitable.</td>
<td></td>
</tr>
</tbody>
</table>
The supply of truth always greatly exceeds its demand

John F Moffitt
Advice

• Don’t let the label ‘responder’ infect your brain
• A ‘responder’ is a patient who was observed to get better by some arbitrary standard
• A ‘responder’ is not a patient who was caused to get better by the drug
• Subsequence is not consequence
• To establish who really responds and who does not you need to work very hard
• You need smart design and smart statistics